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Original Article

A nationwide population study of trazodone use in urology patients

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Abstract

Background: Erectile dysfunction (ED) has been a prevalent disease worldwide. The mainstay of treatment for ED focused on oral medications such as phosphodiesterase-5 (PDE-5) inhibitors or other medical aids with variable acceptance. Trazodone is a second-generation antidepressant approved by the U.S. Food and Drug Administration in 1981. Some evidence has suggested that trazodone may be helpful in improving ED, especially for problems dealing with male arousal. Although controversial, trazodone can sometimes be used for ED as an off-label medication for urological patients. By using a nationwide health insurance database, we attempted to estimate and thereafter analyze the existence and extent of off-label use of trazodone for ED in Taiwan.

Methods: The 1/500 randomly sampled outpatient visits dataset and the 1/1 million randomly selected dataset issued in 2000 in the National Health Insurance Research Database were used to estimate the total number of visits and the urological visits involving trazodone prescriptions. The refill rate, patient age at first prescription, and the diagnoses assigned to the prescription visits were also gathered and analyzed.

Results: The prescription visits in urological clinics consisted exclusively of male patients ($99.0 \pm 1.3\%$, $p < 0.001$). The use of trazodone was more prevalent and regular among the elderly ($p < 0.001$), which happens to parallel the trend of incidence rates of ED. Starting in 1998, the prescription rate for trazodone increased rapidly, but then slowed, equalized, and topped out in 2003. One of the reasons for this marked change in prescriptions rates in Taiwan may be the increased awareness of ED as a treatable disease under the promotion and marketing of three PDE-5 inhibitors. ED-related diagnoses assigned to the prescription visits accounted for 55% of total visits, whereas anxiety/depression-associated diagnoses were the bases of less than 13%, and those attributed to insomnia accounted for 2.3% of visits.

Conclusion: Despite the fact that trazodone was not officially approved for patients with urological conditions, this medication has been used as an ED treatment in Taiwan at least since 1997; the prescriptions of trazodone were more prevalent among the elderly, and this trend increased, then evened out, and eventually reached its maximum point in 2003, correlating with the introduction of PDE-5 inhibitors.

Keywords: erectile dysfunction; National Health Insurance Research Database (NHIRD); population study; trazodone

1. Introduction

Erectile dysfunction (ED) is a worldwide problem. In Taiwan, the prevalence of ED is estimated to be 29% among men older than 40 years.[1] The treatment of ED was challenging prior to the development of phosphodiesterase-5 (PDE-5) inhibitors. Many drugs have reportedly been used to treat ED, including trazodone.[2] The use of trazodone to treat ED, especially for arousal problems, has not been approved in Taiwan; it is indicated as an antidepressant in Taiwan and as a hypnotic in several other countries.[3] Although controversial, it is believed that trazodone has been used for some time as an off-label medication for ED or arousal problems in urological patients.

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In the present study, we demonstrated the trazodone prescription patterns in urological clinics in Taiwan, using information derived from the National Health Insurance Research Database (NHIRD), a prospectively collected database open to qualified researchers. We believe that our research represents the first nationwide, cross section study of trazodone use within the urological specialty.

2. Methods

The National Health Insurance Program single payer system was launched in Taiwan on March 1, 1995. Since its inception more than 15 years ago, more than 98% of the island's population has received nearly all forms of health care services under the program. For research purposes, NHIRD data are derived from this system by the Bureau of National Health Insurance in Taiwan and maintained by the National Health Research Institutes. Each year, the Bureau of National Health Insurance collects information, including registration files and original claims for reimbursement, into larger data files. Data that could be used for identification of patients and care providers is scrambled prior to database reconstruction and prior to being released to researchers. We also followed the related research regulations of the National Health Research Institutes and those of our hospital in the present study. The Details of Ambulatory Care Orders Dataset (DACOD) and the Longitudinal Health Insurance Database 2000 (LHID 2000) of the NHIRD were used for our data analysis. The DACOD database includes all the ambulatory orders, including laboratory examinations and medications. The dataset was at first sampled randomly on a scale of 1:500 to reduce the data size; trazodone use in all clinics and in urological clinics was then identified, stratified by year from 1997 to 2008. The LHID 2000 is an official cohort dataset containing all the original claim data of 200,000 individuals randomly sampled from the year 2000 Registry for Beneficiaries of the NHIRD. There were no statistically significant differences between the LHID 2000 and all enrollees according to the National Health Research Institute's reports. Patients with trazodone prescriptions each year, the patient age at first prescription, and the diagnoses for urological visits with trazodone were processed from the LHID 2000. These patients were further subgrouped into adolescents (<20 years old), young adults (≥20 years old but <40 years old), adults (≥40 years old but <60 years old), and the elderly (≥60 years old). A frequent user of trazodone was defined as a user who obtained at least three refills of trazodone from urological clinics.

According to our clinical experiences, ED patients are customarily designated with the International Codes of Disease-9, Clinical Modification (ICD-9 CM) 607.84 (impotence of organic origin), 302.7 (psychosexual dysfunction), and 302.9 (unspecified psychosexual disorder) in Taiwan. These codes have been used in this study to represent patient diagnosis. ICD-9 CM 296 (affective psychoses), 300 (neurotic disorders), and 311 (depressive disorder, not elsewhere classified) were the codes defined as anxiety/depression-related diagnoses. ICD-9 CM 307.40 (nonorganic sleep disorder, unspecified), 307.41 (transient insomnia), and 307.42 (persistent insomnia) were used to represent insomnia in the present study. ICD-9 CM 607.3 was the code for priapism.

The data were analyzed using the Mann−Whitney test, Kruskal−Wallis test, and Pearson's Chi-square test, with ActivePerl 5.12.1 software from ActiveState (Vancouver, BC, Canada). A p value <0.05 was defined as statistically significant.

3. Results

A total of 20,269 outpatient visits with prescriptions for trazodone were identified from the 1/500 randomly sampled DACOD from 1997 to 2008. In all clinics, women (51.6 ± 2.6%) received the medication significantly more frequently than men (48.3 ± 2.5%, $p = 0.009$). By contrast, male patients (99.0 ± 1.3%) accounted for the large majority of patients receiving trazodone in urological clinics under all kinds of diagnoses ($p < 0.001$), although the rate of usage declined dramatically since 2004 (Fig. 1).

There were 514,069 male patients in LHID 2000, and 4676 patients had visited urological clinics for trazodone prescription, for a total of 18,052 visits. Among these 4676 patients, up to 55.1% were assigned with a code for ED-related conditions. Of the total, 7.8% had both the diagnosis codes for anxiety/depression and ED, and 4.5% were diagnosed with anxiety/depression-related disorders. Only 2.3% of patients were coded with insomnia (Fig. 2). There were 21 patients diagnosed with priapism after the prescription of trazodone, which had an estimated incidence of this potentially adverse effect of 0.45%.

Among those receiving trazodone from urological clinics without ICD-9 CM codes of ED or anxiety/depression (about 30.2% of all patients), the ratio of patients taking daily dosage between 25 mg and 50 mg was 22.0%, 34.0%, or 32.3% if we assumed that the prescription duration was 7 days, 14 days, or 28 days, respectively. That is, the trazodone use rate in urological clinics (at a lower dose for insomnia) was estimated to be about 6.7−10.4%; however, when it came to patients taking trazodone solely under the ED diagnosis (55.1% of all patients), the estimated ratio of patients taking low dose of trazodone was 19.3%, 38.1%, or 37.0%, respectively.

The prescription and new prescription rates of trazodone use in urology outpatients in Taiwan were also estimated from the LHID 2000 (Fig. 3). The mean prescription rate from 1997 to 2008 is 0.117 ± 0.033%, peaking in 2002 (0.155%). The mean new prescription rate from 1998 to 2008 is 0.086 ± 0.023%, which achieved its maximum in 2003 (0.114%). The most prevalent use of trazodone was noted among the elderly, as well as the incidence rate, but both started to decline after 2003. Adolescents had the lowest use rate of all groups.

Frequent use accounted for 26.60% of all trazodone prescriptions in urological clinics and 87.1% of frequent users started taking trazodone after 40 years of age. Of all trazodone prescriptions, 48.0% were coded with ED only and 9.4% were diagnosed with depression only. Patients with ED and

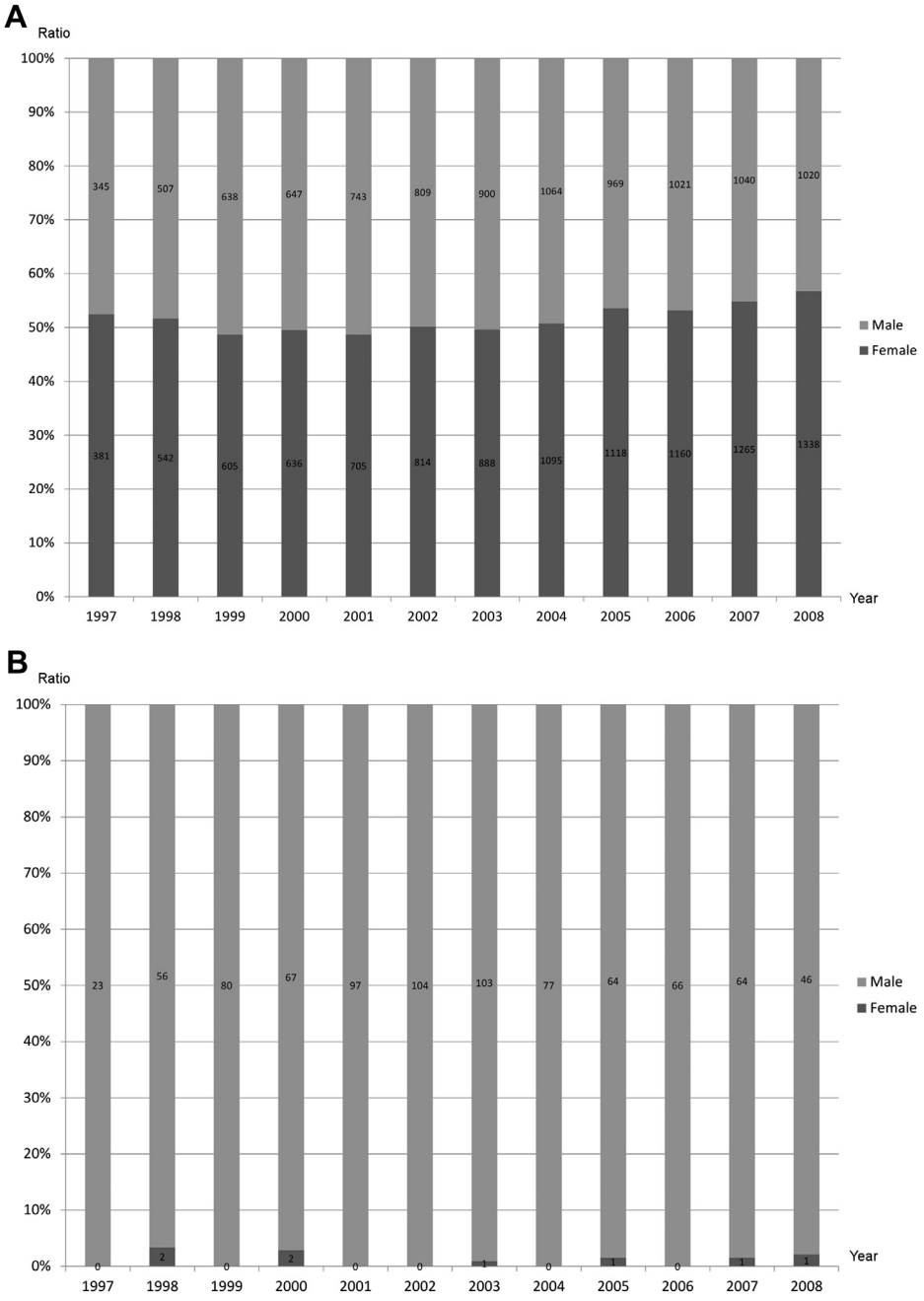

Fig. 1. Yearly trazodone use in total and urological visits. In all clinics (upper), women (mean 51.6 ± 2.6%) received the medication significantly more frequently than men (mean 48.3 ± 2.5%, $p = 0.009$); in urological clinics (lower), male patients (mean 99.0 ± 1.3%) accounted for the vast majority receiving trazodone ($p < 0.001$). Numbers in each bar are the absolute prescription numbers by years.

depression accounted for 18.3%. A positive correlation between the rate of frequent use and the patients' age was demonstrated with Chi-square test ($p < 0.001$), from 3.57% in adolescents to 33.31% in the elderly (Fig. 4).

4. Discussion

ED, defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance,[4] has been a prevalent problem worldwide. In Taiwan, a recent questionnaire-based study estimated the prevalence rate of ED up to 27% among Taiwanese men more than 30 years of age, and 29% among those older than 40 years.[1] ED may deteriorate overall life satisfaction and health-related quality of life, especially in the emotional, relational, and sexual domains.[5,6] Moreover, the relationship between ED and depressed mood may be bidirectional: the presence of either condition may trigger or exacerbate the other; for example, ED could contribute additional distress to patients with depression, resulting in prolonged or worsened depressive illness, and subsequent noncompliance with the treatment.[7] There were also interactions between the treatments for both conditions.

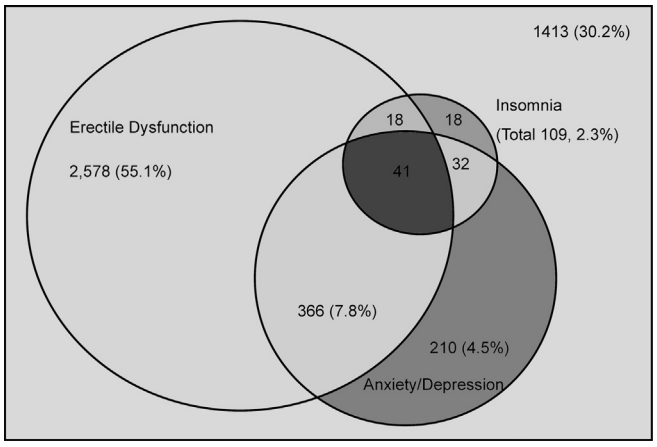

Fig. 2. Diagnoses for trazodone use in urological male patients. Up to 55.1% were assigned with code with ED-related conditions; 7.8% had both the diagnosis codes for anxiety/depression and ED, and 4.5% were diagnosed with anxiety/depression-related disorders. Only 2.3% of patients were coded with insomnia.

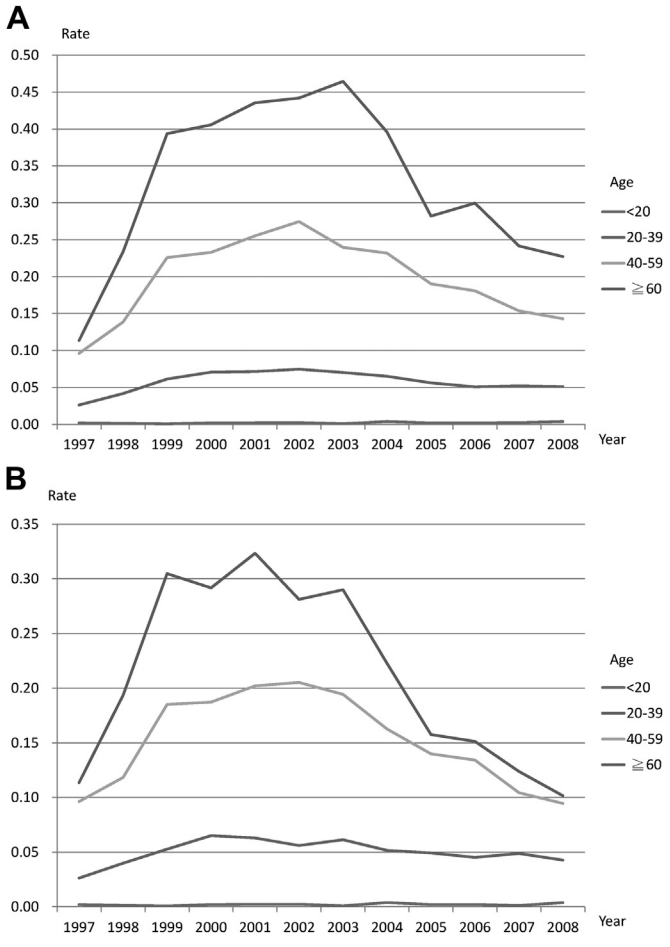

Fig. 3. Current and new trazodone prescription trends for male Taiwanese each year, stratified by age. The mean prescription rate from 1997 to 2008 is 0.117 ± 0.033%, peaking in 2002 (0.155%). The mean incidence rate is 0.086 ± 0.023%, which achieved maximum in 2003 (0.114%). The most prevalent use of trazodone was noted among the elderly, as well as the incidence rate, but both started to decline since 2003. Adolescents had the lowest use rate of all groups.

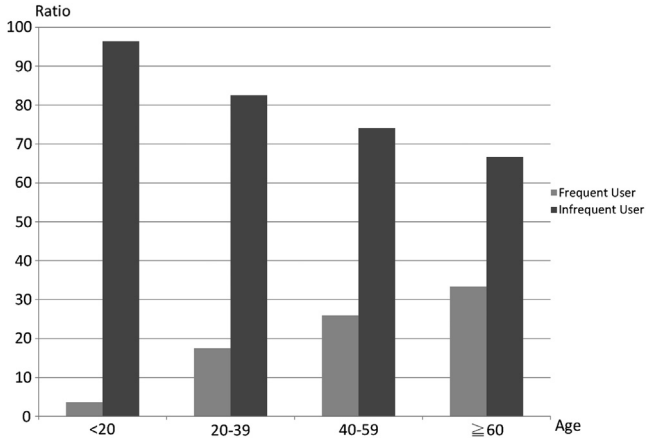

Fig. 4. Frequent versus infrequent refill of trazodone in urological male patients. A positive correlation between the rate of frequent use and the patients' age was demonstrated with Chi-square test ($p < 0.001$), from 3.57% in the adolescents to 33.31% in the elderly.

Selective serotonin reuptake inhibitors, the most popular antidepressants, are highly associated with the side effect of ED.[8,9]

Treatment options for patients with ED include psychosexual therapy, penile prostheses, revascularization, vacuum constriction devices, intracavernous injection, transurethral, and oral drug therapy.[10] Jarow et al[11] have shown a patient preference for less invasive treatment for ED (such as oral or transurethral drug therapy) despite the higher satisfaction rate with alternatives that involve surgical intervention.

Trazodone hydrochloride possesses antidepression effects by acting as a serotonin antagonist reuptake inhibitor. It was noted to cause enhanced libido and priapism.[12–14] In one animal study, this erectogenic effect may result from its primary metabolite, *m*-chlorophenylpiperazine, interacting with the 5-HT1C receptor.[15] Several studies then reported that trazodone can be an option for selected patients with psychogenic ED at higher doses.[2,16–19] However, debate continued regarding the prescription of trazodone for ED,[20,21] and it has no indication for ED in Taiwan. Thus, trazodone for ED treatment is an "off-label use."

Off-label use means the use of a medication or device deviating from what is mentioned in its U.S. Food and Drug Administration product label. It is common, legal, and an important source of innovation; however, it can be costly and strong evidence of the efficacy and safety of the drug for its off-label use may be lacking.[22] The Food and Drug Administration generally prohibits off-label indications from being promoted to physicians and consumers, but not prescriptions by physicians. There are different, conflicting points of view in the health care system when it comes to off-label use—the pharmaceutical industry seeks to enlarge product markets, and payers such as the National Health Insurance doubt the need to pay for unproven and costly products. The public had demonstrated that it wants medications not only to be safe and effective, but further wants access to the newest therapies. To be autonomous and also meet the needs of individual patients are the wishes of many physicians. Ineffectiveness of the off-

label use or unpredictable adverse effects may occur; consequently, thorough and comprehensive communication should be made by physicians to their patients, to most effectively address the individual needs of patients and provide detailed explanation of the off-label prescription for informed consent.

What was the true condition of trazodone use in the field of urology under strict payment regulations? Depression-related disorder, the only indication for trazodone in Taiwan, is more prevalent in young adults, especially female patients.[23] From this study, the gender distribution of trazodone prescription in all clinics between 1997 and 2008 was comparable with that of depression-related disorder. When urological clinics were involved, trazodone was used exclusively by male patients; moreover, frequent male users got their first trazodone prescriptions in urological clinics primarily after their 40s. These findings showed that trazodone was not used for depression-related diagnoses. The gender and age distribution of prescriptions in urological clinics in Taiwan was compatible with the prevalence of ED in Taiwan.[24] From the tentative diagnoses assigned for prescriptions with trazodone by urologists, we could prove that trazodone use in the urological field in Taiwan was mainly for ED during the period investigated: more than 50% of male patients received their trazodone prescriptions for ED-related diagnoses; only 4.5% of trazodone use originated from anxiety/depression-related diagnoses (Fig. 2). However, this trend was difficult to confirm strictly from dosage differences because we could only obtain information on the total amount not the exact daily dose of a drug from LHID 2000. The ratio of patients taking trazodone at a lower dose under the isolated diagnosis of ED was similar or even higher than the ratio of patients without ED and anxiety/depression diagnoses. It seems that, in high proportion, urologists in Taiwan treat patients with ED with trazodone at a low dose.

The first phosphodiesterase type-5 (PDE-5) inhibitor [sildenafil (Viagra)] has been available in Taiwan since March 1999. The other two PDE-5 inhibitors currently available in the country [vardenafil (Levitra) and tadalafil (Cialis)] have been in the market since November 2003. Although these drugs are excluded by National Health Insurance coverage, they have had an extraordinary influence on the diagnosis and treatment of ED. Kaye and Jick[25] demonstrated a 2- to 3-fold increase in the annual incidence of ED in the United Kingdom during 1998−2000. A similar condition can be seen in Taiwan, where the introduction of sildenafil prompted more men to be aware that ED is a curable disease and to seek treatment. Jiann et al[26] reported that the yearly sales of sildenafil in Taiwan in 1999 reached 1,085,116 tablets, which increased 136% in 2002 (up to 2,566,512 tablets). With the launch of sildenafil in 1999, the new users of alprostadil injection almost doubled from 1999 to 2002 in their institute,[26] similar to the observed trend of trazodone prescription in urological clinics in our study. A retrospective study by Sullivan et al[27] also disclosed a rise in prescriptions issued for ED after the introduction of sildenafil, which reached a plateau after 12−15 months. If trazodone was used merely as an antidepressant in male urology patients, there should not be a steep increase and a plateau in its prescription and new prescription from 1997 to 2003. After vardenafil and tadalafil started to be sold in Taiwan, the prescription of trazodone in urological clinics declined because of more treatment choices, as well as the acceptance of PDE-5 inhibitors by the public. The correlation between the introduction of sildenafil and the boost in trazodone prescriptions precisely demonstrated how trazodone was used as a choice for ED treatment during the investigated period.

Theoretically, trazodone should be more suitable for young psychogenic impotent patients without major organic findings.[2] However, frequent users in the present study were generally older than 40 years. It is possible that, for younger patients, improvement in erectile function from taking several doses of trazodone could break the vicious cycle of performance anxiety. It is also possible that, for the elderly, cardiovascular disease with concomitant use of nitrate discouraged urologists from prescribing PDE-5 inhibitors, thus rendering trazodone as the available treatment option for these less physically fit patient population. Constitutionally there are more old men in urological clinics, as well as higher rates of insomnia among the elderly, both of which are possible reasons.

There are several limitations to this study. First, we could not demonstrate the interrelationship between prescribing PDE-5 inhibitors and trazodone in the same cohort population, because PDE-5 inhibitors are not covered by National Health Insurance. Second, other confounding factors affecting trazodone prescriptions could not be totally excluded. Third, the placebo effect of trazodone as a treatment choice for ED is difficult to evaluate. Fourth, the change in government policy and the spread of new research results about the effect of trazodone for ED among urologists from 1997 to 2008 would also affect the prescription of this medication. Lastly, the NHIRD, a database derived from registration files and claim data for reimbursement, lacked information about daily dosage or patients' response.

However, off-label use of trazodone as a treatment of ED in urological clinics in Taiwan did exist. Although debate continues about the effectiveness of trazodone for the treatment of ED, apparently some urologists in Taiwan view it as a treatment choice for ED, under the risk of payment rejection; moreover, some patients with ED in Taiwan visit urological clinics, asking for trazodone for their ED more than one time. This provides a hint that trazodone may be effective in certain patients. Previous research concerning trazodone as a treatment for ED was mainly based on Caucasian populations. Whether there is racial difference in response to trazodone is unknown, and who would benefit from off-label use of trazodone requires more investigation. However, this population-based research applying administrative database can be a stepping stone to further research on trazodone use in Asian patients with ED, providing an additional choice for ED treatment for those who could not tolerate or have contraindications for PDE-5 inhibitors. Clinicians should continue to monitor patients on trazodone for rare but significant adverse effect of priapism, and further when new drug combinations

involving trazodone are considered. Patients need to be educated to increase their awareness of the side effects of trazodone, and report any such effects early to best impact long-term morbidity. Further clinical trials may be warranted to investigate the safety and effectiveness of trazodone, as well as the optimized dosage for ED.

In conclusion, from the NHIRD, we demonstrated a correlation between the introduction of PDE-5 inhibitors and the frequency of prescription of trazodone from 1997 to 2008. Prescription use, although uncommon, was more prevalent among the elderly, rather than among the younger patients. It is likely that trazodone was used primarily for treatment of ED rather than anxiety/depression or insomnia in the urological field in Taiwan. However, the safety, cost-effectiveness, and optimized dosage of trazodone as an oral alternative for patients with ED need further investigation.

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